FATTY LIVER INDEX IN GENERAL POPULATION VISITING THE MASTER HEALTH CHECKUP IN A TERTIARY CARE CENTRE

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By

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DECLARATION

I, Dr.P.PREETHA, solemnly declare that this dissertation "FATTY LIVER INDEX IN A GENERAL POPULATION VISITING THE MASTER HEALTH CHECK UP IN A TERTIARY CARE CENTRE" is a bonafide record of work done by me in the Department of general surgery, PSG institute of medical sciences and research ,Coimbatore. under the guidance of Prof.DR.K.JAYACHANDRAN M.D.

This dissertation is submitted to the Tamilnadu Dr.M.G.R.Medical University, Chennai in partial fulfillment of the University regulations for the award of MD Degree (General Medicine) Branch-I, Examination to be held in April 2012.

Place: Coimbatore

Date: **(Dr.Preetha.P)**

CERTIFICATE

This is to certify that the dissertation work entitled "FATTY LIVER INDEX IN A GENERAL POPULATION VISITING THE MASTER HEALTH CHECK UP IN A TERTIARY CARE CENTRE" submitted by Dr.P.PREETHA is work done by her during the period of study in this department from 30/05/2009 to 29/05/2012. This work was done under the guidance of Dr.K.JAYACHANDRAN, Professor, Department of medicine, PSG IMS&R.

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CONTENTS

INTRODUCTION

The term NAFLD was coined by Ludwig et al in 1980, it is a spectrum of liver diseases with histologic features of alcohol – induced liver disease that occurs in individuals who do not consume significant quantities of alcohol.

The spectrum includes

1) Fatty liver (hepatic steatosis)

2) NASH – Non alcoholic steatohepatitis

3) Cirrhosis

Clinically NAFLD is a diagnosis of exclusion of other causes of liver disease . It is characterized histologically by excessive accumulation of hepatic fat in the absence of alcohol consumption . NAFLD is a major cause of liver related to morbidity and mortality. A complete diagnosis of fatty liver disease ideally should define the histology, including the stage and grade of the disease as well as its etiology. It is commonly associated with metabolic syndrome. 80% patient with metabolic syndrome have NAFLD .The risk factors for non alcoholic steatohepatits are obesity , type 2 diabetes mellitus , drugs, female gender, hypertriglyceridemia, hypercholesterolemia. Most patients with fatty liver have insulin resistance.

Since the prevalence of fatty liver is increasingly seen in East Asian and India than in western countries this study includes the calculated data for finding the at risk group in our population.

EPIDEMOLOGY

The prevalence of NAFLD varies from 10 – 24 % in general population. Fatty liver has been documented in 10 – 15 % of normal population and 70 -80% of obese population. NAFLD in the general population ranges from 9.3 to 29% in Asia [1]

The prevalence of NAFLD varies due to difficulty in diagnosis. Population based studies have revealed that NAFLD is more common in men than in women . Recent studies have shown that NAFLD has a more even distribution between men and women.9most cases occurs in 4^{th} and 6^{th} decade . In a population-based study in the United States, Browning et al found that individuals with magnetic resonance spectroscopy defined-NAFLD were slightly older (46 versus 45 years old, $p = 0.003$) than those with normal[2] Of particular concern is that NAFLD is increasing in the pediatric population with a prevalence of 3 % in normal children and 20 - 50 % in obese children [3] Familial clustering occurs in NAFLD. The causes of such familial clustering include both genetic and environmental factors. A clear-cut pattern of inheritance of risk for NAFLD was not identified [4] Several instances of fatty liver also have been described in patients with

rare familial disorders (e.g., hypobetalipoproteinemia) diabetes and hemolytic anemia due to a deficiency of red cell Mg2_–adenosine triphosphatase. In such cases, despite the presence of an underlying familial disorder, no systematic studies of the prevalence of fatty liver or steatohepatitis in the affected families have been reported.

Hispanics, East Asians and Indians are more predisposed ethnic groups compared to Caucasian and afro Americans. In one study , the estimated prevalence ranges from 3% to 24%.5 NAFLD is extremely common among patients undergoing bariatric surgery, ranging from 84% to 96%. In these patients, 25% to 55% have NASH, 34% to 47% have fibrosis, and 2% to 12% have bridging fibrosis or cirrhosis.

The Dallas Heart Study of more than 2200 adults documented hepatic triglycerides content by proton magnetic resonance spectroscopy and found fatty liver in 31% of participants , the highest prevalence (45%) among Hispanics.[2]

Population based estimates of NAFLD have been reported for other countries as well , these studies have documented NAFLD in 10% to 24% of the population with 76% among obese non – drinkers The prevalence of NAFLD is 50% in people with diabetes , 74% in obese and nearly 100% in morbidly obese individuals [6] NAFLD is a independent risk factor for cardiovascular mortality. More recently, several biopsy studies among both

living and cadaveric liver donors have been published. The prevalence of NAFLD among living liver donors ranges from 17.9% in Japan [7,8]

PATHOGENESIS

Hepatic steatosis is caused by imbalance between the deliver or synthesis of fat in the liver .It is complex , potentially involving multiple tissues including the liver , adipose tissue muscle and other peripheral tissues.in the presence of excess calories,the rates of lipolysis and lipogenesis are affected , leading to release of free fatty acids into circulation this influences the accumulation of lipids in liver and peripheral tissues.and cytokines are released and impair insulin signaling and reduce insulin mediated glucose uptake. All these are accompanied by impaired apolipoprotein B 100 and formation of very low density lipoprotein.All these factors trigger lipid accumulation and oxidation in the liver , oxidative stress, the release of inflammatory cytokines, and hepatic stellate cell activation.

NASH develops as a consequence of two hit process First hit is accumulation of free fatty acids and triglycerides within liver . Second hit is fatty accumulation leading to chronic oxidative stress

Mechanism of first hit steatosis – insulin sensitivity of adipocytes depends on profile of adipokines – TNF alpha , leptin, adipokinin,sex

hormones,fatty acids , resistin and cortisol. A number of these adipocytokines have been linked to alterations in insulin sensitivity, including adiponectin, leptin, resistin, and tumor necrosis factor-α (TNFα). In addition, many of the same signaling molecules have been shown to be associated with suppressed hepatic insulin sensitivity, and it is thought that adipocytokines may contribute to the development of
liver fibrosis.

Fundamental deficits in NAFLD seem to insulin resistance that lead to impairement in insulin – mediated release of free fatty acids from adipose tissue Increased uptake of fatty acids by hepatocytes leads to mitochondrial beta oxidation overload with consequent accumulation of fatty acids within hepatocytes.

In free fatty acids delivery and reesterificetion to triglycerides overwhelms ability to form and export VLDL , TGL accumulates in liver . In fact, a recent study found that about 26% of hepatic TG accumulation in NAFLD patients could be accounted for by *de novo l*ipogenesis 11 FFA induces gluconeogenesis pathway and inhibits glucose utilization, this leads to increase glucose level , leading to hyperinsulinemia.

Hyperinsulinemia increases synthesis of fatty acids in hepatocytes by increasing glycolysis and increases accumulation of triglycerides by decreasing hepatic production of apolipoprotein B 100 , thus insulin

resistance leads to accumulation of ft in hepatocytes by two mechanisms 1) peripheral lipolysis 2) hyperinsulinemia.

Mechanism of second hit steatohepatitis –

The final common pathway for development of steatohepatitis is oxidative stress within hepatocytes Oxidative stress results from generation of ROS and deficient of antioxidant defences .In a vitro study , incubating hepatocytes with free fatty acids increases their ROS production 12 .Any cause of increased hepatic TNF alpha in NASH will lead to increased mitochondrial ROS production. Peroxidation of plasma and intracellular membranes may cause direct cell necrosis, or apoptosis and megamitochondria ,while ROS induced expression of FAS – Ligand on hepatocyte may induce fratricidal cell death. The aldehyde end products of lipid peroxidation can covalently bind to hepatic proteins and initiating a potentially injurious immune response.[13] Reactive oxygen species mediated lipid peroxidation potentially explain all of the typical histological features of NASH . a key role for lipid peroxidation in the pathogenesis of NASH would also explain the association between steatosis and risk of necroinflammation and fibrosis as in animal models and NASH , the degree of lipid peroxidation correlates with the severity of steatosis [13] Fatty acids in hepatocytes induce to increase in cytochrome P 450 2E1 and 4A activity,which leads to lipid peroxidation, cytokine induction and Fas ligand induction leading to hepatocyte death by activate collagen synthesis by stellate cells and activates tissue transglutaminase. Increased hepatic expression of the Cytochrome P 450 2 E 1 has been shown in both the methionine – choline deficient diet animal model of NASH [14,] CYP 4 A enzymes can become major catalysts of hepatic

microsomal lipid peroxidation.sanyal et al have suggested that increased mitochondrial beta oxidation of FFA may be important source of ROS in NASH [15].ROS deplete hepatic antioxidants and allow accumulation of more ROS . Depletion of antioxidants like paraoxanase may enhance hepatic damage in steatosis .kupffer cell dysfunction induced by insulin resistance leads to increased phagocytic activity , decreased anti inflammatory IL 10 and increased proinflammatory interferon gamma ,IL 6 activity, thus increasing necroinflammatory activity.

Progression of fibrosis – stellate cell activation is via non cytokine pathway or cytokine pathways. TNF alpha stimulates secretion of profibrogenic cytokines like IL 6 , TGF beta , PDGF. Studies in alcoholic fatty liver and NASH have shown that the severity of fat correlates with the degree of hepatic stellate cell activation.16, 17 .these are principal cells in the liver responsible for production of extra cellular matrix proteins and leading to fibrosis cytokines are capable of producing all of the classical histological features of NASH including hepatocyte cell death or apoptosis (TNF alpha) , neutrophil chemotaxis (IL 8) HSC activation and mallory bodies formation (TGF beta)[18]

Role of genetic factors in NASH is suggested by two recent reports of family clustering [19]

REVIEW OF LITERATURE

Conditions Associated With Steatohepatitis

1. Alcoholism
2. Insulin resistance a. Syndrome X i. Obesity ii. Diabetes iii. Hypertriglyceridemia iv. Hypertension b. Lipoatrophy c. Mauriac syndrome
3. Disorders of lipid metabolism a. Abetalipoproteinemia b. Hypobetalipoproteinemia c. Andersen's disease d. Weber-Christian syndrome
4. Total parenteral nutrition
5. Severe weight loss a. Jejunoileal bypass b. Gastric bypass c. Severe starvation
6. Iatrogenic a. Amiodarone b. Diltiazem c. Tamoxifen d. Steroids e. Highly active antiretroviral therapy
7. Refeeding syndrome
8. Toxic exposure a. Environmental b. Workplace

Grading and Staging of NAFLD

The histologic grade indicates the activity of the steatohepatitic lesion, whereas the stage reflects the degree of fibrosis.

Grading NAFLD
1. Macrovesicular steatosis Grade 0:None Grade 1:Up to 33% Grade 2:33%–66% Grade 3: _ 66%
2. Necroinflammatory activity
Grade 1 (mild) Steatosis up to 66%, occasional ballooned hepatocyte (mainly zone 3), scattered intra-acinar neutrophils (PMN) _ lymphocytes, no or mild portal inflammation
Grade 2 (moderate) Steatosis of any degree, obvious zone III ballooning degeneration, intra-acinar PMNs, zone III perisinusoidal fibrosis may be present, mild to moderate, portal and intra-acinar inflammation
Grade 3 (severe) Panacinar steatosis, widespread ballooning, intra-acinar inflammation, PMNs associated with ballooned hepatocytes, mild to moderate portal inflammation
Staging NAFLD 1. Stage 1 Zone III perisinusoidal/pericellular fibrosis; focally or extensively present 2. Stage 2 Zone III perisinusoidal/pericellular fibrosis with focal or extensive periportal fibrosis 3. Stage 3 Zone III perisinusoidal/pericellular fibrosis and portal fibrosis with focal or extensive bridging fibrosis 4. Stage 4 Cirrhosis

In a retrospective analysis, those with florid steatohepatitis characterized by fat, ballooning degeneration, Mallory bodies, or perisinusoidal fibrosis had a poorer long-term outcome than those with fat and only nonspecific lobular inflammation. In another study, Brunt et al. scored a total of 10 findings to develop a grading and staging system for NASH shown above. 20, 21

These included hepatic macrovesicular steatosis, hepatocellular ballooning, intra-acinar inflammation, portal tract inflammation, Mallory's hyaline, acidophil bodies, glycogen nuclei, lipogranulomas, and hepatocellular iron. It was found that the serum alanine aminotransferase (ALT) levels correlated with the severity of the grade of steatohepatitis. 22,23,24

RISK FACTORS

The risk factors for developing NASH are similar risks for benign steatosis.

OBESITY

After exclusion of other risks like alcohol, diabetes ,protein malnutrition and drug toxicity, obesity alone is a major risk for the development of this syndrome 25.the prevalence of obesity in patients with

NAFLD is reported to vary from 30- 100% .in obese patients(BMI > 30) the risk of NAFLD is elevated 4.6 fold .clearly the most significant risk factor for development of NASH . lobular hepatitis was found in 8.7% in patients in a large series of morbidly obese individuals about to undergo surgical small bowel bypass as a treatment for obesity. At autopsy , NASH was found in 18.5 % of obese patients.the prevalence of NASH is 3 % in lean population, but rises to 19% in obesity and nearly 50 % in morbidly obese individuals .NAFLD is more common in individuals with an abdominal concentration of fat with lower BMI .26,27,28 Visceral obesity, as operationally defined by a large waist circumference, is also considered a risk factor for NAFLD 29,30 Visceral adipose tissue is more biologically active than subcutaneous adipose tissue and is known to release greater quantities of adipocytokines. Visceral adipose tissue is a better predictor of altered liver function and insulin resistance than obesity defined by body mass index Of obese individuals found to have NASH at autopsy, of which most cases were not suspected ante mortem, 13.8% had bridging fibrosis or cirrhosis. The corresponding figure for lean individuals was 6.6%.32. NASH is almost always a chronic condition and is most frequently associated with obesity (central, as measured by waist circumference, and overall, as measured by body mass index [BMI]) and type 2 diabetes mellitus.33.

A correlation among BMI , degree of steatosis and severity of liver injury has been demonstrated in several studies . The risk and severity of

NAFLD increases with the number of components of metabolic syndrome . 34, Studies have shown a significant correlation between the risk of the metabolic syndrome , degree of hepatic steatosis, and hip waist ratio , thus highlighting the importance of intra abdominal or visceral fat as predictor of NAFLD .35,36

DIABETES

It is frequently associated with hepatic steatosis .it is found in about , 1/3 of non obese persons with type 2 diabetes at autopsy.NAFLD is strongly associated with type 2 DM and glucose intolerance, wih or without superimposed obesity.

Patient found to have hepatic steatosis by usg examination are more likely to have glucose intolerance and elevated baseline insulin levels. circulating insulin levels found in type 2 diabetes patients may be a least partly responsible for the accumulation of fat in the liver. Hyperglycemia , insulin resistance , hyperinsulinemia , glucose intolerance and type 2 have been described in 25 – 75 % of adults patients with NASHand may increase the risk of NASH more than two foldcompared with that of non – diabetics.the prevalence of NAFLD in diabetic patients may also increase the risk of cardiovascular disease significantly. . IR is defined as a condition in which higher-than-normal insulin concentrations are needed to achieve normal metabolic responses or, alternatively, normal insulin

concentrations are unable to achieve normal metabolic responses Hyperinsulinemia appears as a consequence of the inability of insulin to induce its effect on glucose metabolism, and hence, an abnormally large amount of insulin is secreted to achieve a biological response with consequent several abnormalities in target organs such as the liver, endothelium, and kidneys, and this represents the main feature in the metabolic syndrome.37,38

The metabolic and cellular mechanism(s) linking insulin resistance to NAFLD are not fully understood. Two studies have found decreased insulin extraction by the liver, which contributes to hyperinsulinemia in patients with NAFLD [39,40] NAFLD is strongly associated with type 2 DM and glucose intolerance with or without superimposed obesity. Increased serum insulin and glucose levels also promote *de novo* lipogenesis by upregulating lipogenic transcription factors. NAFLD may in turn result in hepatic IR, which is thought to be triggered by hepatic FFA accumulation and their metabolites that may exacerbate overall IR. Type 2 DM , hyperglycemia, glucose intolerance has been described in 20% - 75% adult patients with NASH and increases the risk of NASH more than 2 fold compared with that of non – diabetic persons .The association between type 2 DM and NAFLD appears strongest in morbidly obese patients.

HYPERLIPIDEMIA

Hyperlipidemia has been found in a substantial proportion of patients with NAFLD .Data from dallas heart study revealed NAFLD in 60% of patients with mixed hyperlipidemia. Study from korea of potential living donors showed that hyperlipidemia was associated with a greater than 2 fold risk of significant (>30%) steatosis .Hyperlipidemia has been thought to be a risk factor or clinical marker for development of hepatic steatosis and NASH [41]

GENDER

In early surveys , female gender was overemphazised and has been refuted . The prevalence of NASH is equal in among men and women at autopsy and prevalence of hepatic steatosis found by CT imaging [42].

DRUGS

NAFLD has been associated with many drugs and toxins and metabolic , surgical and genetic condition, that have abnormal fat metabolism and mitochondrial injury . Drugs like corticosteroids,estrogens,tamoxifen,amiodarone, diltiazem. Cytotoxic drugs like methotrexate, bleomycin, azaserine,tetracycline. There is increasing appreciation of lipoatrophy and severe hyperlipidemia

associated with development of fatty liver in patients being treated with highly active antiretroviral drugs (e.g.,indinavir). This has been associated with the development of severe insulin resistance [43,44,45.] Occupational exposure to several types of chemicals (e.g., organic solvents and dimethylformamide) are also associated with fatty liver disease.

IN ASSOCIATION WITH METABOLIC SYNDROME

NAFLD is now recognized as the hepatic component of the metabolic syndrome , which includes hyperlipidemia , glucose intolerance , obesity and systemic hypertension.the metabolic syndrome is generally defined as 3 or more of the following given table below.although an association between different metabolic abnormalities had been noted for several years, The metabolic syndrome was first publicly described in 1988 by Reaven. 50. Then called Syndrome □, the metabolic syndrome consisted of a cluster of metabolic abnormalities, including obesity (especially abdominal obesity), insulin resistance, impaired glucose metabolism, dyslipidemia, and elevated blood pressure. The metabolic syndrome is estimated to affect about 25% of the adult population. The best available definition

Risk Factor	Defining Level
Abdominal obesity, given as waist circumference	
Men	>102 cm (40 in)
Women	>88 cm (35 in)
HDL cholesterol	Men< 40 mg/dL
	Women< 50 mg/dL
Triglycerides	>150 mg/dL
Blood pressure	>130/>85 mm Hg
Fasting glucose	>110 mg/dL

WHO Clinical Criteria for Metabolic Syndrome

Insulin resistance, identified by 1 of the following: ● Type 2 diabetes ● Impaired fasting glucose ● Impaired glucose tolerance ● or for those with normal fasting glucose levels (_110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions
Plus any 2 of the following: ● Antihypertensive medication and/or high blood pressure (_140 mm Hg systolic or _90 mm Hg diastolic) ● Plasma triglycerides _150 mg/dL (_1.7 mmol/L) ● HDL cholesterol _35 mg/dL (_0.9 mmol/L) in men or _39 mg/dL (1.0 mmol/L) in women ● BMI _30 kg/m2 and/or waist:hip ratio _0.9 in men, _0.85 in women ● Urinary albumin excretion rate _20 _g/min or albumin:creatinine ratio _30 mg/g

Patient with metabolic syndrome have a 4 -11 fold higher risk of developing NAFLD . Recent findings suggest that components of the metabolic syndrome are integrally involved in the pathogenesis of this two hit model. The metabolic syndrome is linked to inflammation and oxidative stress [49] , and it has been demonstrated that individuals with the metabolic syndrome have increased lipid peroxidation [46. 47] The prevalence of metabolic syndrome in patients with NAFLD ranges from 18 % - 67 % depending on body weight.

The risk of NASH is elevated threefold . It is largely believed that insulin resistance is the central feature in the development of the metabolic syndrome. NAFLD is highly prevalent in the general population, is not associated with SLD, but is associated with many features of the metabolic syndrome. (HEPATOLOGY 2005;42:44-52.)48 . The relationship between NAFLD and the metabolic syndrome is becoming increasingly recognized.

Approximately 90% of patients with NAFLD have ≥ 1characteristic feature of metabolic syndrome and about 33% have the complete diagnosis, placing NAFLD as the hepatic representation of the metabolic syndrome[51] In the absence of obesity and diabetes, hyperinsulinemia and insulin resistance are associated with NAFLD [52] In clinical series, individuals with the metabolic syndrome are at greater risk for NAFLD, but no data are available at the population level, and the relative

contribution of each component of the metabolic syndrome to the risk of NAFLD is unknown.

Hamaguchi and colleagues' study clearly demonstrates the very strong relationship between NAFLD and the metabolic syndrome. Approximately one third of the patients in this study with NAFLD met the criteria for the metabolic syndrome, which is very similar to its reported prevalence in Italian patients with NAFLD .

A previous study from Japan demonstrated new onset of fatty liver in 14.3% of 35 519 participants who had repeated liver ultrasonography over a 12-year period (14). The development of fatty liver was associated with an increase in BMI of 1 kg/m2 (around 2 to 3 kg), suggesting that relatively small changes in body weight may exert significant metabolic effects [53.]

In Marchesini and colleagues' Italian study of 304 patients with NAFLD but not overt
diabetes (16), the presence of the metabolic syndrome conferred a higher risk for NASH (odds ratio, 3.2 [95% CI, 1.2 to 8.9]) and a high risk for advanced fibrosis (odds ratio, 3.5 [CI, 1.1 to 11.2]).[54]

Another important finding from the current study was that steatosis regressed in 16% of patients, although this was less likely in the presence of the metabolic syndrome. Regression was associated with was associated

with a small weight loss. Insulin resistance and systemic hypertension, features of the metabolic syndrome, are independently associated with advanced forms of NAFLD. Moderate alcohol consumption seems to reduce the risk of NAFLD in the severely obese, possibly by reducing insulin resistance.55. It clearly shows that the metabolic syndrome and weight gain are risk factors for the disease and for newonset cases. Hamaguchi and colleagues' findings support the possibility that NAFLD might be reversible if BMI and aspects of the metabolic syndrome are managed effectively, even without normalization of weight.

In addition to the components of the metabolic syndrome previously noted, NAFLD has been associated with several rare disorders of lipid metabolism (e.g., abetalipoproteinemia82) and some rare syndromes characterized by severe insulin resistance (e.g., lipoatrophic diabetes and Mauriac syndrome) The liver disease in abetalipoproteinemia as well as lipodystrophy can progress to advanced fibrosis and cirrhosis. NAFLD has also been associated with Weber-Christian syndrome. The biochemical basis for NAFLD in such syndromes and their natural history are unknown and may be variable.

CAUSES OF NON ALCOHOLIC FATTY LIVER DISEASE.

Causes of macrovesicular steatosis
Insulin resistance and hyperinsulinemia Obesity Type 2 DM
Drugs Corticosteroids Estrogens Tamoxifen Amiodarone chloroquine nifidipine and diltiazem
Metabolic – Wilson disease
Nutritional Starvation Protein deficit (kwashiorkor,eating disorders) Choline deficiency Excess carbohydrate
Infections – chronic hepatitis C (especially genotype 3)
Miscellaneous Indian childhood cirrhosis Jejunoileal bypass.

Causes of microvesicular steatosis	
Drugs Valproic acid	Depletion of mitochondril Co A, beta oxidation and blockade of beta oxidation enzymes by P450
Tetracycline	Inhibited beta oxidation , impaired hepatic triglyceride secretion.
Aspirin	Uncoupling oxidative phosphorylation, depletion of extramtrochondrial acety Co A , which prevents transport of fatty acids into the mitochondria.
Nucleoside analogs	Inhibition of mitochondrial DNA replication.
Toxins Ethanol	Diminished mitochondrial NAD impairs beta oxidation stress damages DNA
Toxic shock syndrome	Unknown bacterial toxins
Genetic defects Acute fatty liver of pregnancy	Defects in the beta oxidation ; LCHAD defect in a subset of patients
Beta oxidation defects CPT I CPT 11 Ornitine transcarbamylase deficiency	Inadequate substrate for beta oxidation Inadequate substrate for beta oxidation Inhibition of long and medium chain fatty acid beta oxidation by ammonium.
Others Reye syndrome Cholestasis	Combined acquired and genetic defects in beta oxidation or ureagenesis Impaired mitochondrial function by bile acids.

Microvesicular steatosis is distinguished from macrovesicular steatosis on well defined morphologic grounds and also by pathophysiologic mechanisms.whereas macrovesicular steatosis is caused by an imbalance in the hepatic synthesis and export of TAG , all causes of microvesicular steatosis is retained in smaller vesicles distributed pancellularly rather than coalescing into large droplets characteristic of macrosteatosis is unknown.

CLINICAL FEATURES

Most patients with NAFLD present because abnormal serum transamminase levels are discovered incidentally for screening purposes. In general patients with NAFLD are aymptomatic .if present , symptoms tend to be non – specific and constitutional but may include right upper quadrant discomfort. The most common finding of liver disease is hepatomegaly, which has been reported in up to 50% of subjects in different studies. Of the various stigmata known, the presence of spider nevi and palmar erythema are most common.48 Jaundice, edema, asterixis, and signs of portal hypertension occur in those with advanced cirrhosis. Muscle wasting may occur as the liver disease in more advanced stages.

Clinical and laboratory features of non alcoholic fatty liver disease

Symptoms	Signs	Laboratory features
Common None (48 % - 100% of pts)	Hepatomegaly	Two to three fold elevation of serum ALT and AST levels or AST/ALT ratio less than 1 ,serum alkaline phosphatase level is slightly elevated in one third of patients.,normal bilirubin and prothrombin levels
Uncommon Vague right upper quadrant pain Fatigue Malaise	Splenomegaly Spider angiomata Palmar erythema ascites	Low titre ANA Elevated transferring saturation HFE gene mutation.

Hepatomegaly has been described in upto 75 % of patients with NAFLD . As with many other types of chronic liver disease, most patients with NAFLD in cross-sectional studies are asymptomatic.

In many asymptomatic subjects, elevated ALTlevels are discovered when a hepatic panel is ordered to monitor subjects treated with antihyperlipidemic drugs. NAFLD is the most common cause for unexplained persistent elevation of ALT levels once hepatitis C and other known causes of chronic liver disease have been excluded 56.

Fatigue is probably the most commonly reported symptom and does not correlate well with the severity of the histologic lesion. The development of ascites, anasarca, variceal hemorrhage, or symptoms of hepatic encephalopathy indicates decompensated cirrhosis jaundice occurs late in the course of NASH and indicates advanced liver disease.

LABORATORY FEATURES

In hospital-based populations of patients with NASH, most subjects (50%–90%) have abnormal aminotransferase activities. The degree of enzyme elevation is not marked and is usually between 1 and 4 times the upper limit of normal values the serum ALT level usually is greater than the AST levels ,in contrast with the pattern of alcoholic hepatitis. The AST/ALT ratio is almost never >2. ALT values do not correlate with the degree of steatosis or fibrosis. .The alkaline phosphatase and gamma glutamyl transpeptidase levels may be elevated , but the serum bilirubin levels , prothrombin time and serum albumin level typically are normal , except in patients with NAFLD – associated cirrhosis. Circulating concentrations of the liver transaminases, ALT, AST, and to less extent γ-glutamyltransferase (GGT) are commonly used as markers of NAFLD for many years.

Elevated levels are considered a consequence of liver damage due to fatty acid infiltration and inflammatory stimuli, and recent findings indicate that serum levels of these enzymes are associated with multiple

components of the metabolic syndrome. Increases in ALT are positively associated with each component of the metabolic syndrome, increased TG, glucose, waist circumference, diastolic blood pressure, and reduced HDL-C levels[19]. In addition, insulin resistance, the prevalence of severe liver steatosis, and ALT values have been found to be significantly higher in subjects with the metabolic syndrome compared to those with less than three of the five clinical features considered for its diagnosis[39]. Recent data published from NHANES found significant association with increased ALT and insulin resistance, type diabetes, and the metabolic syndrome[40]. GGT, a less specific marker of liver function, is linked to obesity, hypertension, sedentary lifestyle, hyperinsulinemia, dyslipidemia, inflammation, and oxidative stress 57Furthermore, GGT concentrations have been found to be associated with hypertension in individuals with central adiposity57 suggesting the potential for a pathogenic link among fatty liver disease, endothelial dysfunction, and cardiovascular risk.58 Serum and hepatic iron levels may be elevated in patients with NAFLD ,in particular serum ferritin may be elevated in 20 – 50 5 of patients with NAFLD In a diabetic subject with NASH, isolated hypoalbuminemia may also occur due to proteinuria related to diabetic nephropathy. Hematologic parameters are usually normal unless cirrhosis and portal hypertension lead to hypersplenism. Across several series,15,102,103 about 10%–25% of patients have been noted to have a positive antinuclear antibody, a marker of autoimmunity. The significance of this observation is unclear. About

30%–50% of patients with NASH have either diabetes or glucose intolerance.

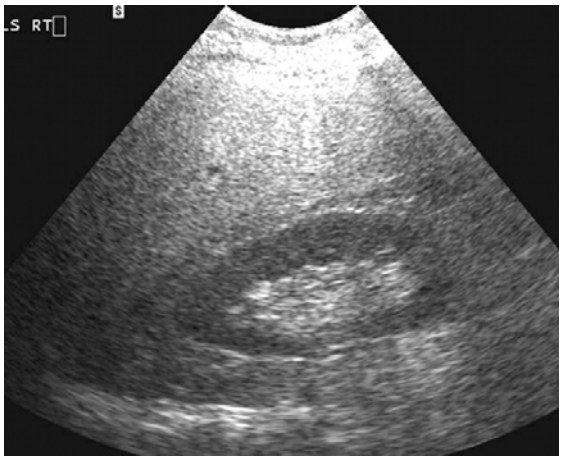
A fasting lipid profile shows hypertriglyceridemia in 20%–80% of patients.59 ,60 Estimating insulin resistance is best measured by rigorous technique such as the euglycemic insulin clamp method , since this test is difficult in routine clinical environment , simpler tests have been sought . several generally accepted methods of approximating the insulin sensitivity has been developed based on the product of the fasting insulin multiplied by the fasting glucose . two of the most commonly used, the homeostasis model (HOMA – IR) and quantitative insulin sensitivity check index (QUICKI), rely on this product and are mathematically related. Mean HOMA index increases with the stage of fibrosis and could help to differentiate stages of fibrosis . An even simpler method is that a product of fasting insulin multiplied by fasting insulin > 700 may indicate insulin resistance .due to lack of standardization of insulin assays makes these difficult to compare. 61.

DIAGNOSIS

The diagnosis of NAFLD requires the exclusion of alcohol abuse; a daily intake as low as 20 g in female subjects and 30 g in male subjects may be sufficient to cause alcohol-induced liver disease in some patients (350 mL [12 oz] of beer, 120 mL [4 oz] of wine, and 45 mL [1.5 oz] of

hard liquor, each contain 10 g of alcohol). The workup of NAFLD and NASH also includes checking into drug abuse, HBV and HCV infections, haemochromatosis, autoimmune liver disease and, in younger patients, Wilson's Disease. In special groups of NASH may be accompanied by drug- and alcohol-induced liver disease and by HCV and HBV infections. The combination of NAFLD/NASH and HCV infection plays a particularly important clinical role because in this situation the rate of liver fibrosis is increased and the success of antiviral therapy is diminished . NASH can be induced by various drugs and toxins including corticosteroids, NASH can be induced by various drugs and toxins including corticosteroids,amiodarone, methotrexate, tetracycline, tamoxifen, and valproate Thus, one needs to carefully assess the full clinical history of patients. In practice NAFLD is often diagnosed by combining elevated levels of ALT and gamma-GT with the sonographic appearance of an increase in the echodensity of the liver.

Ultrasound of the liver has a high sensitivity and specificity (both approaching 90%) for detection of fatty infiltration but does not allow assessment of the presence or degree of inflammation and fibrosis. Therefore, diagnosis of fat in the liver is easily made by ultrasound but diagnosis of NAFLD or NASH can not be made without a liver histology. Conventional radiology studies used in the diagnosis of fatty liver include ultrasound (US), computed tomography (CT), and magnetic resonance (MR) imaging . US can identify hepatic steatosis with reasonable accuracy.



Typical criteria used to assess for steatosis include hepatorenal echo contrast, liver brightness, deep posterior beam attenuation, and vascular blurring Hamaguchi et al used a 6-point scoring system based on liver brightness, attenuation, and vascular blurring on US to evaluate for NAFLD and showed 100% specificity and 91.7% sensitivity when compared with liver biopsy 62

C T has shown a similar diagnostic yield similar to US. Unenhanced CT is accurate in predicting steatosis of greater than 30%, but has been shown to be much less accurate in predicting lower-grade steatosis 63. Diagnostic accuracy has been improved with unenhanced CT scan using liver:spleen attenuation ratios with up to 100% specificity and 82% sensitivity for hepatic steatosis greater than 30%.Hepatic steatosis may be quantified from MR imaging based on the signal differences between fat and water and shows good correlation with microscopic fat content

A novel finding of increased dorsocervical lipohypertrophy in patients with NAFLD was described recently by Cheung et al.

Interestingly, dorsocervical lipohypertrophy was found to be the single greatest contributor to the severity of histologic findings of steatohepatitis and may prove to be a useful tool in the diagnosis of NASH.64.

Although efforts to use noninvasive imaging studies to accurately grade NAFLD in terms of NASH have been unsuccessful, the investigations that use imaging to stage fibrosis in patients, and thus identify those with advanced disease, have shown more promise. Transient elastography is an ultrasound-based technology that is used to measure liver stiffness. In a recent study of 68 patients with NAFLD, a stepwise increase in elasticity was shown with severity of hepatic fibrosis.35 This study showed good correlation between liver biopsy fibrosis stages 1–4 and liver stiffness using ROCs with positive predictive values (PPVs) between 64% and 93.5% for the varying stages of fibrosis.

Liver biopsy remains the best diagnostic tool for confirming NASH, as well as the most sensitive and specific means of providing important prognostic information. It is also useful to determine the effect of medical treatment, given the poor correlation between histological damage and the results of liver tests or imaging studies . Today most pathologists use the Brunt description to score the histological degree of NASH The histological features of NAFLD are indistinguishable from those of alcohol-induced liver disease. There are two lesions associated with NAFLD: (i) predominantly macrovesicular steatosis alone or (ii) predominantly macrovesicular steatosis and varying amounts of cytologic

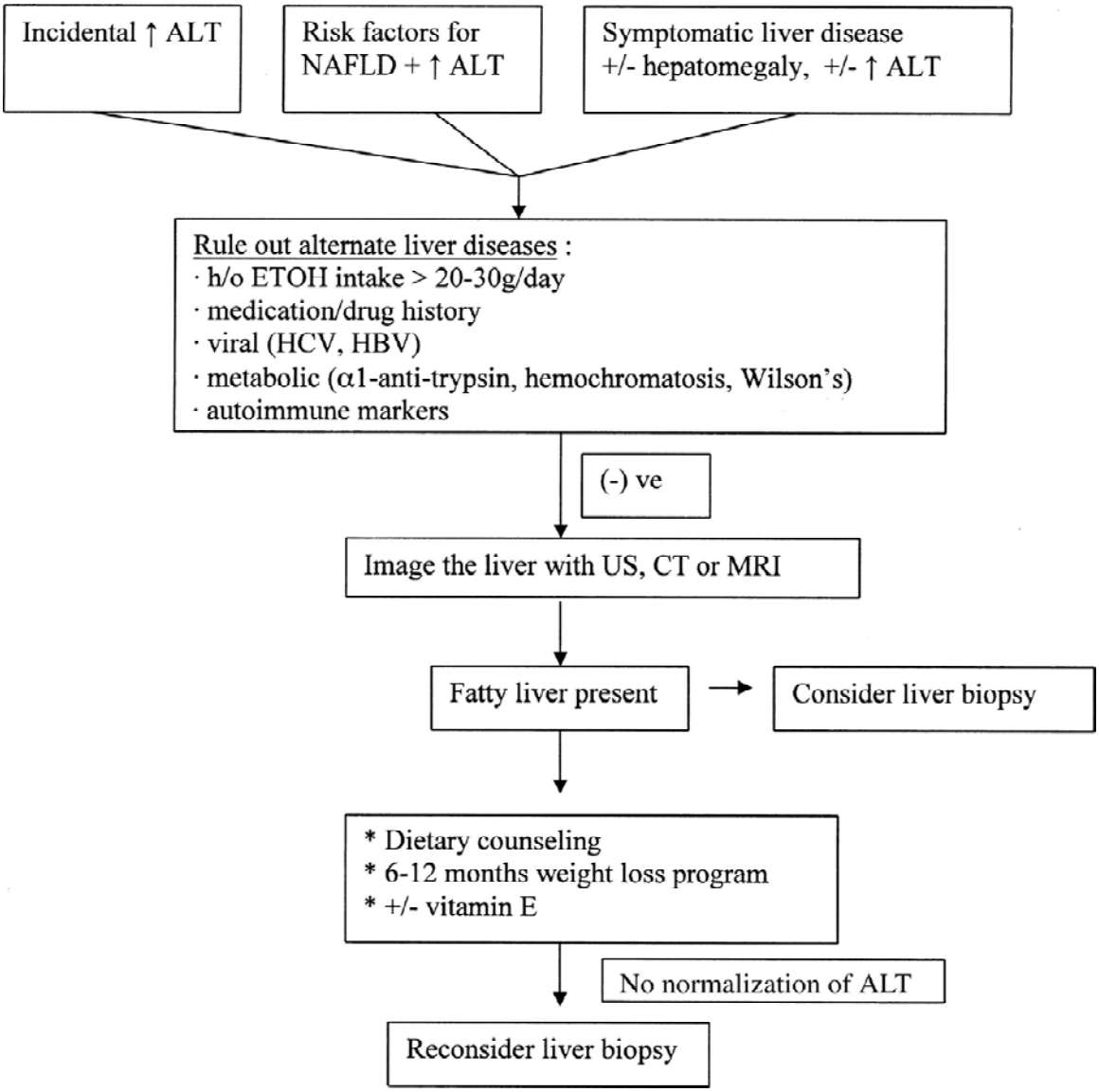
ballooning and spotty necrosis, scattered mixed neutrophilic–lymphocytic inflammation, glycogen nuclei, Mallory's hyaline, and perisinusoidal fibrosis (NASH). All of the features of steatohepatitis are not present in every instance of steatohepatitis. The severity of steatosis can be graded on the basis of the extent of involved parenchyma. Brunt's classification is a system that unifies the steatotic and necroinflammatory lesions into a "grade" and the types of fibrosis into a "stage".

Grade	Steatosis	Ballooning of hepatocytes	Degree of inflammation
1	<33 %	Minimal	Mild
2	34 – 66%	Present	Moderate
3	>66%	Marked	Portal – moderate

Stage	Fibrosis
1	Perisinusoidal
2	Perisinusoidal,portal,periportal
3	Bridging septa
4	Extensive bridging fibrosis, cirrhosis.

Some factors can help to identify patients with NAFLD in whom the liver biopsy may provide the most prognostic information. An age of 45 years or more, the presence of obesity or type 2 DM, and a ratio of AST/ALT are noteworthy indicators of advanced liver fibrosis. In the subgroup of overweight patients with BMI >25, older age, higher BMI, and higher levels of ALT and triglycerides are also indicators of more

advanced liver fibrosis. In severely obese patients with BMI >35, an IR index >5, systemic hypertension, and an elevated ALT level correlate strongly with the presence of steatohepatitis, whereas hypertension and raised levels of ALT/AST and C-peptide suggest the presence of advanced fibrosis81. Both the decision to perform a liver biopsy in clinical practice and the timing of the biopsy must be individualized and should include the patient in the decision-making process.



Scoring Systems for Identifying NAFLD

Scoring systems using one or several clinical and/or laboratory parameters to identify patients with NASH from the larger pool of NAFLD patients also have been assessed. Palekar et al 62 developed a clinical model that sums 5 risks factors for NASH identified on multivariatelogistic regression. These factors include age 50 or older, female sex, aspartateaminotransferase (AST) level of 45 or greater, BMI of 30 or greater, AST/ALT ratio of 0.80 or greater, and hyaluronic acid level of 55 or greater. Combining 3 or more of these factors yielded a sensitivity of 73.7% and a specificity of 65.7% for detecting NASH with an ROC of 0.763. This study provided a relatively simple means of identifying NASH patients but requires further validation in a larger study population 65. One of the early scoring systems developed called the body mass index; age at liver biopsy; alanine aminotransferase; and serum triglycerides (BAAT) score used 4 easily determined clinical variables to assess for hepatic fibrosis 66.

The development of the FibroTest-FibroSURE (Biopredictive) based on _2- macroglobulin, apolipoprotein A1, haptoglobin, total bilirubin, and _-glutamyltransferase levels.66 A 90% negative predictive value (NPV) for advanced fibrosis and a 70% PPV for advanced fibrosis were noted in final analysis. 67. A recent review by Guha et al70 tabulated 29 studies

that looked at noninvasive markers of hepatic fibrosis in NAFLD either as primary or secondary end points. This comprehensive review identified the key variables found in the majority of these studies, which included the presence of diabetes, increasing age, increased homeostatic insulin resistance, increased AST/ALT ratio, decreased platelets, hyaluronic acid, and BMI. Although these models are good in predicting advanced fibrosis at any one time point

TREATMENT

Much like the biomarkers being studied to diagnose NASH noninvasively, current therapies are focused on the various pathways thought central in the pathogenesis of this disease the only effective treatment for NAFLD and NASH is a slow and moderate weight loss. Several studies have shown that rapid weight loss (very low calorie diet or starving) increases the risk of progression of liver disease and even liver failure Patients should therefore be educated not to induce rapid weight loss, but to aim at a weight loss of less than 10% of their body weight over 6-12 months. it is more important that the patients simply eat healthy foods like vegetables and fruits, rich in fibre and complex carbohydrates with a low glycemic index; they should avoid meat, saturated fat and products with less complex carbohydrates. Data have shown that in the setting of obesity, moderate weight loss of approximately 6% via caloric restriction improves insulin resistance and intrahepatic lipid content. Furthermore, caloric restriction improves serum aminotransferase levels and hepatic

histology. A small study by Anderson et al74 showed that extreme weight loss via starvation leads to worsening liver histology, including fibrosis. In addition, 2 bariatric surgery studies have shown mild worsening of lobular inflammation and fibrosis in a subset of patients with a mean weight loss of 32 and 38 kg, respectively. Huang et al85 counseled patients to follow a 1400 kcal/day diet for 12 months in 15 biopsyproven NASH patients with a subsequent mean weight loss of 2.9 kg (3% of body weight). Among the 9 of 15 patients (60%) who had a histopathologic improvement on repeat liver biopsy, the average weight loss was 7%.Although it would seem that the preponderance of the evidence supports that moderate caloric restriction resulting in modest weight loss is helpful in improving biochemical parameters, insulin sensitivity, and hepatic steatosis68.69.70.

EXERCISE

Suzuki et al109 found that in a population of 348 male patients who received annual health physicals, regular exercise and weight loss over a 1-year period was associated with a significant improvement in serum aminotransferase levels. Hickman et al111 followed up 3 NASH patients for 3 months with combined dietary modifications and moderate exercise of 150 minutes of aerobic exercise weekly with a mean weight loss of 4% of total body weight. Patients who lost weight experienced improvement in serum aminotransferase levels that were maintained at 15 months of follow-up evaluation provided the weight loss was sustained. Repeat liver

biopsy in 14 patients 3–6 months after lifestyle modification showed significant improvement in steatosis and fibrosis.

DRUGS

There is no drug proven to be beneficial in NAFLD and NASH; therefore no drug has been approved by FDA. drugs that might reverse insulin resistance such as metformin and thiazolidinediones (rosiglitazone, pioglitazone) are the most promising (Angelico 2007); in smaller studies these drugs have shown some histologic improvement of NASH (Bugianesi 2004; Belfort 2006). all drugs that induce weight loss might be beneficial in NAFLD and NASH, in particular when diet and life-style modification do not work. Both sibutramine and orlistat have shown to improve some characteristics of NAFLD and NASH such as the sonographic degree of liver steatosis as well as the histological degree of steatosis and fibrosis (Sabuncu 2003; Derosa 2004, Hussein 2007; Harrison 2007). Orlistat. The reversible inhibitor of gastric and pancreatic lipase, orlistat, appears to be the most studied weight loss medication used in the treatment of NASH. medication is taken with meals and blocks approximately 30% of dietary triglycerides. Zelber–Sagi et al115 showed steatosis only improved in the orlistat group despite significant weight loss in each group. Harrison et al116 obtained repeat liver biopsies at 9 months and showed that regardless of regimen, a 9% body weight reduction produced improvement in biochemical markers, serum aminotransferase

levels, steatosis, and necroinflammation, but no improvement in fibrosis. Antioxidants and cytoprotective substances have also been proposed to treat NAFLD and NASH including vitamin E, vitamin C, glutathione, betaine, acetylcysteine, S-adenosyl-L-methionine and ursodesoxycholic acid. After a recent Cochrane analysis, none of these substances has shown significant benefit in validated randomized studies (Lirussi 2007).

Glucagon-like protein-1–receptor agonist (incretin analogs)**.**

Peptides that are derived from glucagonlike protein-1–receptor agonists such as exenatide also may prove to be potential therapeutic agents in the treatment of NASH. These incretin analogs have been studied extensively in patients with type 2 diabetes mellitus and have been found to promote insulin secretion, suppress inappropriate glucagon secretion, slow gastric emptying, induce satiety, and are associated with modest weight loss .[71.]

Insulin-Sensitizing Medications

Thiazolidinediones improve insulin resistance in skeletal muscle, adipose tissue, and the liver through their action as peroxisome proliferator–activated receptor _ agonists that increase plasma adiponectin levels and fatty acid oxidation and decrease fatty acid synthesis. These agents have been the most studied insulin sensitizers used in the treatment of NASH. A preliminary study of 22 NASH patients (50% with impaired glucose tolerance or diabetes) treated for 48 weeks with rosiglitazone

showed overall improvement in insulin sensitivity and serum aminotransferase levels. Repeat liver biopsy at 48 weeks showed significant improvement in necroinflammation, ballooning, and zone 3 perisinusoidal fibrosis with 45% (10 patients) no longer meeting criteria for NASH. Another pilot study compared pioglitazone 30 mg/day plus vitamin E 400 IU/day with vitamin E alone and showed improvement in steatosis in both groups but improvement in hepatic inflammation and fibrosis in the pioglitazone plus vitamin E arm only.[72.]

Metformin

Metformin is a biguanide that improves insulin sensitivity by decreasing hepatic gluconeogenesis and limiting triacylglycerol production. Animal model data has been promising, with early studies of obese mice given metformin showing improved serum transaminase levels, hepatomegaly, and steatosis.140 open-label RCT in 110 NAFLD patients was performed in Italy that compared metformin treatment with 2 control groups of vitamin E 800 IU/day or a prescriptive, weight-reducing diet.144 Metformin showed higher rates of aminotransferase normalization. Repeat liver biopsy in 31% of the metformin group showed improvement in steatosis, necroinflammation, and fibrosis[74,75.] Overall, the insulin-sensitizing medications show the most promise to date in improving histopathology in patients with NASH.[73.]

Antioxidant therapy

The depletion of antioxidants within hepatocytes resulting in impaired ROS inactivation is the basis for antioxidant supplementation as a potential treatment for NASH. [77] The lipid-soluble antioxidant, tocopherol (vitamin E), has been shown to inhibit lipid peroxidation and suppress inflammatory cytokines such as tumor necrosis factor-_, and its use in the treatment of NASH has been studied. One study comparing 6 months of 1000 IU vitamin E and 1000 mg vitamin C daily vs placebo showed significant improvement in hepatic fibrosis within the vitamin group but not between groups and no change in serum aminotransferase levels or hepatic inflammation [76].

Ezetimibe

Ezetimibe (Zetia, Kenilworth, NJ) is another lipid-lowering medication that may have hepatic benefits in the treatment of NASH. This medication selectively inhibits intestinal cholesterol absorption and in controlled studies with statins appears to lower serum LDL cholesterol by 24% as well as triglycerides by 16%.161 A recent study by Deushi et al showed improved insulin resistance and decreased lipid deposition and fibrosis in obese rats treated with ezetimibe. No clinical trials with this therapy have been published

Liver transplantation for NASH

LTX is the final option for patients with end-stage liver disease due to cirrhosis and complications of portal hypertension with NASH. Due to the increase in the prevalence of NASH, there is also an increase in LTX done for end-stage liver disease caused by NASH. However, NASH can recur after LTX, particularly if patients have previously undergone jejunoileal bypass surgery (Kim 1996; Requart 1995; Weston 1998; Contos 2001; Burke 2004)[79]. LTX does not cure the metabolic defect that causes NASH .

Surgery for obesity

Gastric bypass has also recently been shown to improve NASH (Liu 2007; de Almeida 2006; Furuya 2007) [80] however, surgery is usually restricted to patients with massive obesity .

AIM OF STUDY

1) To determine the fatty liver index in general population by using the potential predictors of fatty liver like age , gender, SGOT, SGPT, GGT, BMI, hip waist ratio , fasting glucose, fasting insulin, triglycerides and serum cholesterol.
2) To help physician to select patients for liver biopsy and to decide on the treatment.
3) To advice intensified lifestyle counseling to high risk individuals.

MATERIALS AND METHODS

This study was conducted at PSG Medical college and hospital, Coimbatore. The study participants were the individuals attending the master health check up clinic and diagnosed to have fatty liver by ultrasonogram.

A total number of 206 were included in the study. They were divided equally into cases and controls based on the presence/absence of fatty liver by ultrasound. This study was done during June 2010 to November 2011. The lab results of the study participants were obtained from the computer database and were used to determine the fatty liver index.

STUDY DESIGN – Prospective case control study.

SAMPLE SIZE

Based on inclusion and exclusion criteria, 104 patients with fatty liver and 104 patients without fatty liver were enrolled. The identification of fatty liver was done by ultrasonographically by hyperechogenicity or brightness of the liver

INCLUSION CRITERIA

Age more than 18 years

Participants diagnosed to have fatty liver in ultrasound abdomen

Non - Alcoholic

Non - Diabetic

EXCLUSION CRITERIA

Alcoholic

Hypothyroidism

Decompensated liver disease

Cirrhosis of liver.

EVALUATION AND INVESTIGATION

BODY MASS INDEX

HIP WAIST RATIO

FASTING INSULIN LEVEL

FASTING LIPID PROFILE

LIVER FUNCTION TEST

FASTING GLUCOSE LEVEL

RESULTS

Table 1 gives the characteristics of the subjects with and without fatty liver

Group Statistics						
age	Fatty liver	103	50.2115	9.63980	.94526	
	No fatty liver	103	52.3365	11.65742	1.14310	0.107
sex	Fatty liver	103	1.3846	.48886	.04794	
	No fatty liver	103	1.4712	.50158	.04918	0.208
insulin	Fatty liver	103	20.1143	10.95720	1.07444	
	No fatty liver	103	21.4413	9.64183	.94546	0.211
LDL	Fatty liver	103	1.3119E2	37.99951	3.72616	
	No fatty liver	103	1.4315E2	47.31402	4.63952	0.319
HDL	Fatty liver	103	36.7788	7.74842	.75979	
	No fatty liver	103	47.8173	10.70683	1.04989	0.000
GGT	Fatty liver	103	1.9084E2	104.06954	10.20486	
	No fatty liver	103	1.4861E2	61.80857	6.06083	0.002
TGL	Fatty liver	103	1.8729E2	52.85475	5.18283	
	No fatty liver	103	1.7017E2	44.55049	4.36854	0.000
SGOT	Fatty liver	103	37.0962	21.34257	2.09281	
	No fatty liver	103	29.4135	11.03710	1.08228	0.132

SGPT	Fatty liver	103	44.5962	35.02967	3.43494	
	No fatty liver	103	30.9327	12.46998	1.22278	0.092
cholesterol	Fatty liver	103	1.3526E2	203.36117	19.94120	
	No fatty liver	103	98.6635	32.62902	3.19954	0.036
BMI	Fatty liver	103	25.7786	2.83749	.27824	
	No fatty liver	103	23.7288	2.60499	.25544	0.000
FBS	Fatty liver	103	1.1776E2	35.51794	3.48282	
	No fatty liver	103	1.4825E2	55.63835	5.45579	0.000
WAIST	Fatty liver	103	1.7160	.51284	.05029	
	No fatty liver	103	.9212	.28985	.02842	0.000

From the above variables - the predictors identified more frequently are HDL (p=0.000), GGT (p=0.002), triglycerides (p=0.000), insulin (p=0.211), BMI (p=0.000), FBS (p=0.000), Hip waist ratio(p=0.000)

Table 2 shows the inclusion of the above selected variables by binary logistic regression analysis with stepwise likelihood ratio method

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	WAIST	-5.032	.701	51.527	1	.000	.007	.002	.026
	Constant	6.275	.865	52.667	1	.000	531.318		
Step 2[b]	HDL	.108	.024	19.991	1	.000	1.114	1.062	1.167
	WAIST	-4.855	.745	42.428	1	.000	.008	.002	.034
	Constant	1.539	1.254	1.506	1	.220	4.660		
Step 3[c]	HDL	.100	.026	14.975	1	.000	1.105	1.051	1.162
	TGL	-.014	.005	9.362	1	.002	.986	.977	.995
	WAIST	-5.926	.986	36.089	1	.000	.003	.000	.018
	Constant	5.172	1.803	8.232	1	.004	176.342		
]\ Step 4[d]	HDL	.107	.029	13.782	1	.000	1.113	1.052	1.177
	TGL	-.024	.007	11.883	1	.001	.976	.963	.990
	FBS	.034	.011	9.441	1	.002	1.034	1.012	1.057
	WAIST	-6.242	1.127	30.698	1	.000	.002	.000	.018
	Constant	2.240	1.994	1.262	1	.261	9.391		
Step 5[e]	HDL	.089	.031	8.060	1	.005	1.093	1.028	1.163

	TGL	-.029	.008	13.962	1	.000	.971	.956	.986
	BMI	-.276	.106	6.806	1	.009	.759	.616	.934
	FBS	.037	.012	9.559	1	.002	1.038	1.014	1.063
	WAIST	-6.418	1.204	28.393	1	.000	.002	.000	.017
	Constant	10.389	3.831	7.353	1	.007	3.250E4		
Step 6[f]	HDL	.098	.035	7.817	1	.005	1.102	1.030	1.180
	TGL	-.028	.008	11.570	1	.001	.972	.956	.988
	GGT	-.020	.007	7.273	1	.007	.981	.967	.995
	BMI	-.370	.126	8.580	1	.003	.691	.539	.885
	FBS	.037	.012	9.318	1	.002	1.038	1.013	1.063
	WAIST	-6.608	1.247	28.097	1	.000	.001	.000	.016
	Constant	15.974	4.920	10.541	1	.001	8.654E6		

a. Variable(s) entered on step 1: WAIST.

b. Variable(s) entered on step 2: HDL.

c. Variable(s) entered on step 3: TGL.

d. Variable(s) entered on step 4: FBS.

e. Variable(s) entered on step 5: BMI.

f. Variable(s) entered on step 6: GGT

The above model based on the 6 remaining predictors fitted well with p value of 0.339 by Homer – Lemeshow statistics,and had a ROC – AUC of 0.00 (95%CI)

These variables were multiplied by using the formula below.

FLI = (e - 0.014*loge (triglycerides) - 0.370*BMI + 0.108*loge (hdl) -5.032 waist circumference +0.037* FBS -0.020* ggt - 15.974) / (1 + e - 0.014*loge (triglycerides) - 0.370*BMI + 0.108*loge (hdl) - 5.032 waist circumference +0.037* FBS -0.020* ggt - 15.974) * 100

The sensitivity and specificity of the ROC curve are shown below

Coordinates of the Curve

Test Result Variable(s):newlogistic

Positive or greater than equal to	Sensitivity	1 – Specificity
-1.0000	1.000	1.000
.0000	.990	1.000
.0000	.981	1.000
.0000	.971	1.000
.0000	.962	1.000
.0000	.952	1.000
.0001	.942	1.000
.0001	.933	1.000
.0001	.923	1.000
.0001	.913	1.000
.0002	.904	1.000
.0002	.894	1.000
.0002	.885	1.000
.0002	.875	1.000
.0008	.865	1.000
.0017	.856	1.000
.0020	.846	1.000
.0023	.837	1.000
.0025	.827	1.000
.0028	.817	1.000
.0036	.808	1.000
.0051	.798	1.000
.0065	.788	1.000
.0083	.779	1.000
.0103	.769	1.000
.0116	.760	1.000
.0122	.750	1.000
.0125	.740	1.000
.0134	.731	1.000
.0149	.721	1.000
.0163	.712	1.000
.0181	.702	1.000

.0196	.692	1.000
.0219	.683	1.000
.0307	.673	1.000
.0380	.663	1.000
.0412	.654	1.000
.0485	.644	1.000
.0631	.635	1.000
.0785	.625	1.000
.0926	.615	1.000
.1028	.606	1.000
.1056	.596	1.000
.1082	.587	1.000
.1336	.577	1.000
.1626	.567	1.000
.1989	.558	1.000
.2418	.548	1.000
.2776	.538	1.000
.3445	.529	1.000
.3901	.519	1.000
.4109	.510	1.000
.4687	.500	1.000
.5317	.490	1.000
.5847	.481	1.000
.6759	.471	1.000
.7529	.462	1.000
.8021	.452	1.000
.8825	.442	1.000
.9338	.433	1.000
.9615	.423	1.000
.9958	.413	1.000
1.0266	.404	1.000
1.0749	.394	1.000
1.1070	.385	1.000
1.2851	.375	1.000
1.7432	.365	1.000
2.3506	.356	1.000
3.0526	.346	1.000

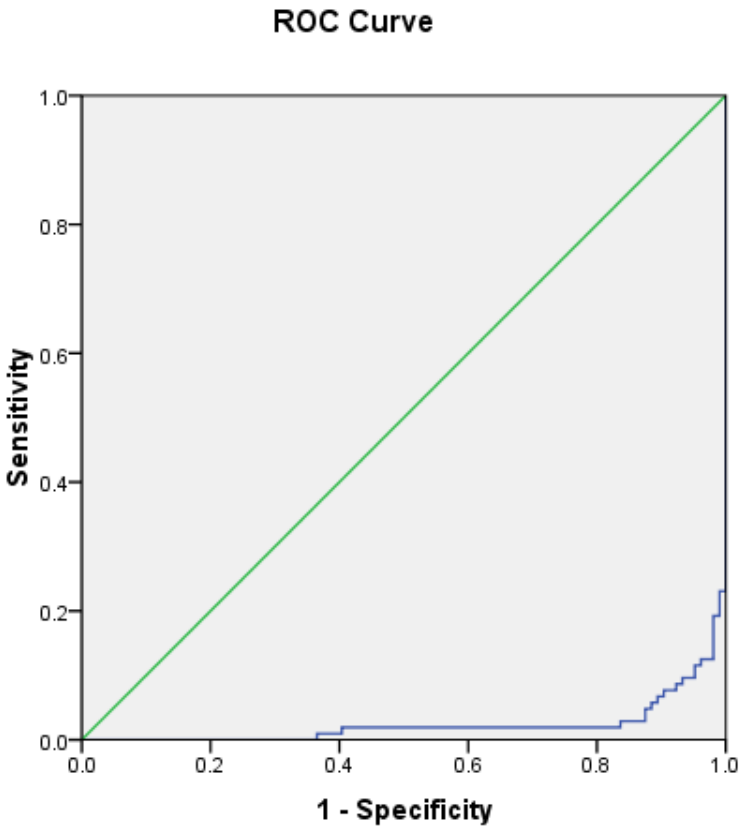
3.6206	.337	1.000
4.1034	.327	1.000
4.4432	.317	1.000
4.9968	.308	1.000
5.7504	.298	1.000
7.1761	.288	1.000
8.6202	.279	1.000
9.2767	.269	1.000
9.7915	.260	1.000
10.2206	.250	1.000
12.1860	.240	1.000
14.0684	.231	1.000
14.6197	.231	.990
15.7139	.221	.990
16.5579	.212	.990
17.5653	.202	.990
18.5365	.192	.990
18.7593	.192	.981
19.8752	.183	.981
21.8772	.173	.981
23.4631	.163	.981
24.3188	.154	.981
25.8106	.144	.981
27.2545	.135	.981
29.6765	.125	.981
31.8883	.125	.971
32.2043	.125	.962
33.0383	.115	.962
33.9315	.115	.952
37.8232	.096	.952
43.3800	.096	.942
46.0001	.096	.933
46.8013	.087	.933
47.2926	.087	.923
49.9636	.077	.923
52.5479	.077	.913
54.0992	.077	.904

60.1028	.067	.904
65.3018	.067	.894
68.5349	.058	.894
72.2352	.058	.885
73.6662	.048	.885
74.4463	.048	.875
74.7570	.038	.875
76.7833	.029	.875
78.9581	.029	.865
79.9972	.029	.856
81.0782	.029	.846
82.5313	.029	.837
84.3945	.019	.837
85.0158	.019	.817
85.0669	.019	.808
85.4709	.019	.798
85.8401	.019	.788
86.0307	.019	.779
86.2424	.019	.769
86.3099	.019	.760
86.6272	.019	.750
87.2522	.019	.740
87.8543	.019	.731
88.1989	.019	.721
88.5121	.019	.712
88.7634	.019	.702
89.1388	.019	.692
89.8402	.019	.683
90.8263	.019	.673
91.7518	.019	.663
92.2325	.019	.654
92.5701	.019	.644
92.8583	.019	.635
93.1609	.019	.625
93.5251	.019	.615
93.8183	.019	.606
93.9942	.019	.596

94.1229	.019	.587
94.2782	.019	.577
94.4994	.019	.567
94.8683	.019	.558
95.3898	.019	.548
95.8015	.019	.538
96.2360	.019	.529
96.5974	.019	.519
96.8645	.019	.510
97.3418	.019	.500
97.6262	.019	.490
97.6303	.019	.481
97.7937	.019	.471
97.9815	.019	.462
98.1589	.019	.452
98.3428	.019	.442
98.3828	.019	.433
98.4189	.019	.423
98.5347	.019	.413
98.6355	.019	.404
98.6561	.010	.404
98.6812	.010	.394
98.7047	.010	.385
98.7643	.010	.375
98.8388	.010	.365
98.8700	.000	.365
98.9018	.000	.356
98.9458	.000	.346
98.9984	.000	.337
99.0733	.000	.327
99.1589	.000	.317
99.2105	.000	.308
99.2596	.000	.298
99.3362	.000	.288
99.4079	.000	.279
99.4902	.000	.269
99.5450	.000	.260

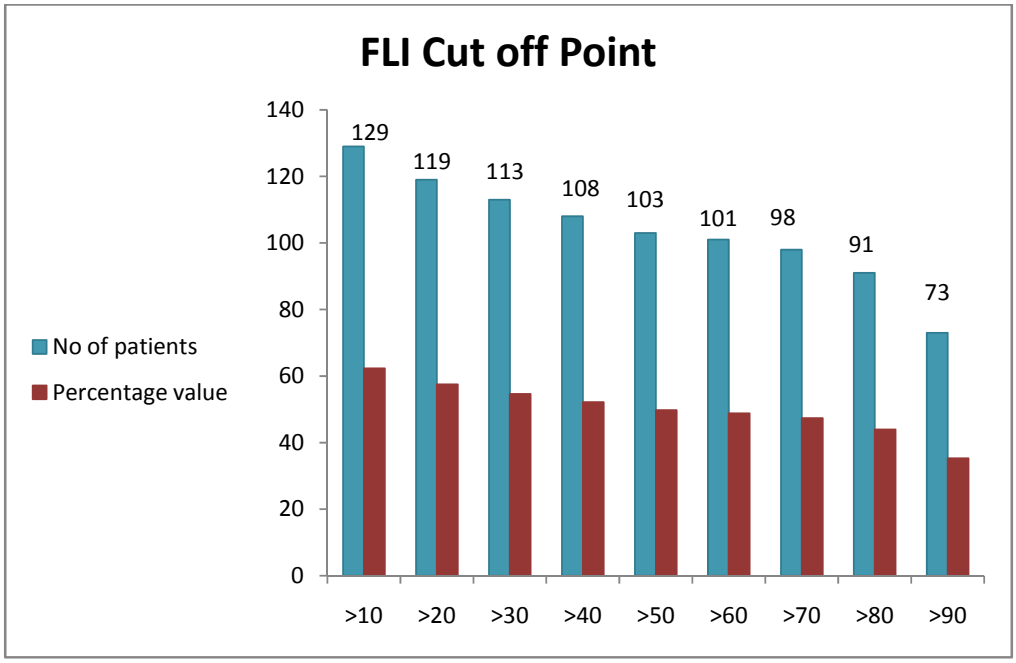
99.5584	.000	.250
99.6461	.000	.240
99.7325	.000	.231
99.7449	.000	.221
99.7504	.000	.212
99.7564	.000	.202
99.7675	.000	.192
99.7774	.000	.183
99.7877	.000	.173
99.8162	.000	.163
99.8391	.000	.154
99.8461	.000	.144
99.8782	.000	.135
99.9042	.000	.125
99.9109	.000	.115
99.9191	.000	.106
99.9297	.000	.096
99.9382	.000	.087
99.9399	.000	.077
99.9445	.000	.067
99.9491	.000	.058
99.9523	.000	.048
99.9565	.000	.038
99.9671	.000	.029
99.9837	.000	.019
99.9960	.000	.010
100.9999	.000	.000

The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.



Based on the ROC value the following table gives the cut – off value.

FLI cut point	No	%
>10	129	62.31884
>20	119	57.48792
>30	113	54.58937
>40	108	52.17391
>50	103	49.75845
>60	101	48.79227
>70	98	47.343
>80	91	43.96135
>90	73	35.2657



As shown above the greatest contribution for FLI was triglycerides, GGT , BMI, hip waist ratio. The above table gives the SN, SP, LR+ and LR- of FLI. A FLI < 30 can be used to rule out .(SN = 54.58 %) and a FLI ≥ 60 to rule in hepatic steatosis(48.79%)

DISCUSSION

The natural history of NAFLD remains poorly understood and the search for non – invasive methods with which to identify patients with advanced fibrosis and cirrhosis remains a key issue .

In this study, we developed a simple non invasive system composed of routinely measured and easily available variables to find the fatty liver index. Our results highlight the utility of a new panel of biochemical markers for detection of Fatty Liver Index.

Among the 103 patients included in this study according to inclusion criteria the major predictors were BMI , hip waist ratio, low HDL levels, triglyceride, GGT and fasting glucose level.

Although age increase the risk of obesity and metabolic syndrome NAFLD is not systematically associated with age. 82. **In this study age is not associated in any of the multivariate models.**

According to gender ,**this study does not support the hypothesis that any specific gender** is a risk factor for NAFLD in the general population which is similarly quoted in a study done in a general population 47.

In a study both normal liver and alcoholic liver disease were less likely seen than NAFLD in obese subjects, 38 confirming that **BMI is an independent predictor of NAFLD**. In this study BMI and hip waist ratio were the strongest predictor of fatty liver in the final model.

Among liver enzymes , **GGT was an independent predictor of fatty liver** while SGOT and SGPT was not associated with fatty liver in this study..In many previous studies an elevated SGPT did discriminate NAFLD either from normal liver or from alcoholic fatty liver , indicating that this enzyme is not an independent predictor of NAFLD . These findings confirmed that there is a high prevalence of NAFLD in subjects without elevated SGPT in general population and that the use of elevated SGPT as a marker of NAFLD has to be discouraged.

Triglycerides were the independent predictor of fatty liver as confirmed by previous studies.83. **Fasting glucose were also a important predictor after exclusion of insulin in this study**.In both normal liver and alcoholic fatty liver hyperglycemia were less likely than in NAFLD , confirming that an altered glucose metabolism is a risk factor for NAFLD . Importantly, hyperglycemia was associated with a greater risk of NAFLD independently from hyperlipidemia even after exclusion of insulin on the contrary insulin was not identified as an independent predictor in this study.

Level of HDL cholesterol were low in this study as confirmed by previous study done in a general population Shangai , China sept 2005 indicated that the prevalence of Obesity, diabetes, hypertension, and dyslipidemia were all significantly higher in fatty liver in patients than in controls. In contrast , the level of HDL cholesterol were markedly lower and our study was done to find if these results are consistent in a Indian population.

As these variables are easily applied this fatty liver index is easy to employ in routine practices. in our population a FLI <30 ruled out and a FLI >60 ruled in hepatic steatosis as detected by ultrasonography

CONCLUSION

- Fatty liver is highly prevalent in our country and is related to multiple metabolic risk factors.
- In conclusion this study shows that BMI, hip waist ratio, low HDL levels, triglyceride, GGT and fasting glucose level are good predictors of fatty liver.
- Hepatic steatosis can be ruled out by using the FLI which is a non invasive tool in a comunity level.

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